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Nanomaterials and the Precautionary Principle

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Kessler (2011) provided a valuable update on the current state of research and regulatory policy concerning nanomaterials. However, the article could give the misleading impression that the precautionary principle constitutes a straightforward guideline for improving public policy in this area. Instead, the precautionary principle provides only a general framework that must be specified before one can adequately assess its implications for policy.

Near the beginning of the article, Kessler (2011) quoted Alexis Baden-Mayer, who worried,

> [I]n our regulation of food and consumer products, we don't implement the precautionary principle. Things go to market before we know whether or not they're really safe for human beings over the long term.

Kessler (2011) concluded with a quotation from Michael Hansen:

> I think we need to take a precautionary approach because we've learned the hard way over and over and over again. You'd think we would learn.

By framing the issues in this way, Kessler (2011) intimated that the precautionary principle could serve as a valuable guide for future research and policy making. However, without further specification, the principle provides only a rough outlook or orientation rather than a specific regulatory plan of action; its merits cannot be clearly evaluated unless a number of further questions are answered.

A number of scholars have attempted to clarify how various formulations of the precautionary principle relate to one another. There are at least three important features that vary in different accounts of the principle: *a*) the threats that ought to be addressed; *b*) the amount and kinds of knowledge necessary to justify precautionary measures; and *c*) the specific precautionary measures that ought to be taken (Elliott 2010; Manson 2002; Sandin 1999). All three issues require further discussion in the case of nanomaterial research and regulation.

Regarding threats, one of the most crucial issues is whether it is sufficient to show that nanoparticles are safe for humans or whether they must also be shown to be safe for the environment—and, if so, what environmental impacts must be tested. Andrew Maynard hinted at this issue:

> I think there is a greater chance that we're going to see long-term environmental impacts from these materials than we are going to see short-term consumer impacts. (Kessler 2011)

Given the vast array of nanoparticles under consideration, it seems doubtful that they could all be thoroughly tested for a wide range of environmental effects before allowing their use.

This raises the question of how much evidence should be demanded before approving particular sorts of nanoparticles. A number of questions are relevant here, some of which are touched on by Kessler (2011): What kinds of screening studies should be required? When should *in vivo* studies be required? What structural or functional changes to a nanoparticle (e.g., size, crystal structure, manufacturing process) should trigger new toxicity studies? Should by-products of the production process also be studied in order to declare a nanoparticle safe (Templeton et al. 2006)? What steps must be taken to ensure that multiple manufacturing batches of the same nanoparticle result in products with the same toxicity profile? Does it matter what kinds of consumer products the nanoparticles are used for?

Finally, although many proponents and opponents of the precautionary principle treat the precautionary principle as if it requires bans on potential threats until they are shown to be safe, a range of other positions are also available on this issue. Three options include *a*) insisting that government agencies be notified when products contain particular nanoparticles; *b*) demanding labeling; or *c*) taking steps to minimize human or environmental exposure to nanoparticles until they have received further testing. Kessler (2011) highlighted our present failure to achieve some of these minimal steps.

These considerations do not by themselves count as sufficient reasons for rejecting the precautionary principle, but they do show that the decision to adopt it is the start of a complicated conversation rather than a straightforward choice about how to regulate nanomaterials.

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Kevin C. Elliott
Department of Philosophy and
USC NanoCenter
University of South Carolina
Columbia, South Carolina
E-mail: ke@sc.edu

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Manganese in Drinking Water and Intellectual Impairment in School-Age Children

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We read with interest the the article by Bouchard et al. (2011) on the effect of manganese in drinking water on children's IQ (intelligence quotient). In this cross-sectional study, the authors examined IQ scores in relation to manganese exposure using four exposure metrics: *a*) concentration of manganese in tap water; *b*) concentration of manganese in hair samples; *c*) estimate of manganese intake from water consumption; and *e*) estimate of manganese intake from diet consumption.

One key finding from the study of Bouchard et al. (2011) is that a higher concentration of manganese in tap water was significantly associated with lower IQ. Compared with the other three exposure metrics used in the study, the concentration of manganese in water followed an almost perfect dose–response relationship with children's IQ, and it was shown to be a better predictor of lower IQ than the exposure metrics. We found this surprising for three reasons. First, in their analysis of the association between concentration of manganese in tap water and IQ, Bouchard et al. included the entire study population (n = 362). We consider this inappropriate because 33% of the study participants (n = 121) did not drink tap water at home. Thus, these 121 children may have experienced much lower exposure to manganese from tap water than the remaining children in the study. Second, if we consider the highest quintile of water-manganese concentration (median, 216 μg/L), the estimated manganese intake from water would be ≤ 0.43 mg/day for half of the children in this exposure group, assuming a daily water intake of 2 L. Even at this level, the intake of manganese from water was still far below the daily intake recommended by the Institute of Medicine (2001): children 1–3 years of age (1.2 mg/day) and children 4–13 years of age (1.5–1.9 mg/day). Third, Bouchard et al. reported that the children's manganese intake from food was more than two orders of magnitude compared to

the amount ingested from water. This suggests that if elevated manganese was causally related to lower IQ, the decrease in IQ was more likely due to the intake of manganese from both water and food sources than from water alone. While one can postulate differences in bioavailability between manganese in food and in water, these would need to be considerable to result in equal or greater uptake from water than from food.

The utility of hair as a biomarker for human exposure to manganese has yet not been established [Agency for Toxic Substances and Disease Registry (ATSDR) 2001]. There is still a lack of standard procedure for collection of hair samples as well as insufficient evidence to demonstrate the effect of washing hair on analytical results (ATSDR 2001). Bouchard et al. (2011) excluded children with dyed hair, but it would be interesting to also distinguish children with natural hair of different colors in the analysis, because levels of manganese in hair can vary by natural colors of hair.

Bouchard et al. (2011) generated an interesting hypothesis on neurotoxicity of water manganese in children at a level that is currently considered to have no adverse effect (World Health Organization 2008), but we believe more studies will be needed to confirm their findings. To better characterize human exposure to manganese from water, it is important for future studies to quantify bioavailability of manganese from water and from food sources. In addition, employing a prospective study design and controlling for all possible risk factors—including overall nutritional status—will be critical. Additionally, comparing hair with other biomarkers of manganese exposure would be another area to explore for future studies.

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Hong Chen
Ray Copes
Ontario Agency for Health Protection and Promotion
Toronto, Ontario, Canada
E-mail: hong.chen@ohapp.ca

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Manganese in Drinking Water: Bouchard Responds

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Chen and Copes raise some interesting issues regarding our article (Bouchard et al. 2011). In our study we investigated the change in IQ scores with respect to different exposure metrics for manganese. One of these metrics was home tap water manganese concentration, which was strongly associated with IQ deficits. Chen and Copes indicate that they consider it inappropriate to include in this analysis children who did not drink tap water at home. Second, they note that even for children in the highest quintile of water manganese concentration, the intake of manganese from water ingestion is below the recommended dietary manganese intake (Institute of Medicine 2001). In response to their first point, it is important to consider that children who do not drink tap water are still exposed through the consumption of many foods and drinks prepared with tap water. In addition, and perhaps most important, children might be exposed by inhalation of aerosols containing manganese when showering (Elsner and Spangler 2005). If this represents a significant source of exposure, which is unclear (Aschner 2006; Spangler and Elsner 2006), inhalation of aerosols could be responsible for inducing neurotoxic effects. Indeed, inhaled manganese is delivered to the brain much more efficiently than ingested manganese, because it bypasses normal homeostatic mechanisms.

Third, Chen and Copes make the point that because dietary intake of manganese intake is much higher than the amount ingested from water, the decrease in IQ is more likely due to intake of manganese from water and food sources collectively, rather than from water alone. The intake of manganese from water consumption was indeed very small compared with dietary intake (medians, 8 and 2,335 μg/kg/month, respectively), but we found no evidence that dietary manganese is related to cognitive abilities. As we reported in our article (Bouchard et al. 2011), dietary manganese intake, assessed with a food frequency questionnaire, was not associated with IQ and did change the point estimates for water manganese concentration when included in the regression model.

We believe that the interpretations that assimilate manganese present in water to dietary manganese have had the effect of dismissing the potential risks of this source of exposure, thus slowing research into this question. Little is known about the absorption and retention of manganese from food versus water, or about inhalation of aerosols in showers. Although more research is necessary to understand the mechanisms by which manganese present in water might be neurotoxic for children, we believe that our findings offer strong support for this hypothesis. Because manganese levels associated with significant cognitive deficits in our study are common in groundwater, this problem could have a great public health importance. For instance, 11% of domestic wells have manganese concentrations > 140 μg/L in the United States (U.S. Geological Survey 2009). We agree that additional studies, ideally with a prospective design, are necessary.

Finally, a valid biomarker of manganese exposure would greatly advance our understanding of this metal's toxic effects. We used hair, notably because its collection is much less invasive than blood sampling. Chen and Copes rightly point out the limitations of hair as a biomarker, and research should explore new biomarkers. For instance, in a small study, saliva manganese levels were significantly higher in welders than in nonexposed subjects, and levels increased in welders with the more years of exposure (Wang et al. 2008). Also in that study, saliva manganese concentrations correlated with serum concentrations. Saliva is less invasive to collect than blood and less prone to external contamination than hair; thus, it might be a useful biomarker.

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Maryse F. Bouchard
Department of Environmental and Occupational Health
University of Montreal
Montreal, Québec, Canada
E-mail: maryse.bouchard@umontreal.ca

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